Section of Obstetrics and Gynæcology

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Uterine Contractility and Cervical Dilatation

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IN outlining the subject of abnormal uterine action in labour, I must do it from the standpoint of the physiologist rather than that of the clinician.

The immediate problem which confronts the uterus at the end of gestation is that of dilating a closed cervix. During pregnancy, the uterus develops sufficient latent power to overcome at a definite future time a definite resistance against which it does not test its strength until the moment of conflict arrives. Cervical resistance involves in the first phase the resistance of the tissues of the cervix to passive stretching but there may be additional resistance arising from a nervous action which, in my opinion, has yet to be defined. Cervical resistance likewise involves inherent individual differences related to uterine growth processes and to previous obstetrical history, particularly parity.

What is the magnitude of the force necessary to cause cervical dilatation? Recent studies in which pressures within the amniotic sac were measured (Alvarez, Caldeyro and Reynolds, 1950) show that when labour proceeds at a normal rate, the absolute pressure developed in the uterus during uterine systole is in excess of 24 mm. mercury, usually between 30 and 70. If uterine systole averages between 16 and 24 mm. mercury, the progress of labour is slow; labour is delayed or prolonged. When, however, this pressure is less than 16 mm. of mercury, the cervix does not dilate. The condition then may be one of false or prodromal labour or of inertia. Admittedly these conclusions are tentative pending more detailed studies. Such studies will recognize the role of parity, fœtal position, uterine load, uterine hypoplasia and the like. The figures mentioned do give us the range of our problem, however. How, one asks, does the uterus achieve the minimum average force necessary to overcome the resisting cervix?

PHYSIOLOGICAL BASES OF CERVICAL DILATATION

There are three basic mechanisms by which a pattern of uterine contractions is achieved which is capable of dilating the cervix. These are morphological, physical (biophysical), and biochemical mechanisms.

The morphological mechanism is concerned with uterine growth processes during pregnancy. There is not time to recount these here, but they have been described recently in another place (Reynolds, 1949). The result of the normal growth processes is to effect in the human uterus at term an advantageous distribution of muscular tissue. The fundus is double the thickness of the cervix and lower uterine segment prior to the beginning of effacement. There is, therefore, a preponderance of contractile power in the fundus.

The power which a muscle can develop is directly proportional to its thickness. This, then, is a first requisite of normal labour yet it is one which uterine hypoplasia or over-distension may negate. The role of such factors as obstetrical faults is not really known.

The physical basis of normal labour is concerned with the relative difference in tissue tension between the opposite ends of the uterus, in the fundus and cervix respectively. The Reverend Samuel Haughton, M.D., was the first to describe this in 1873 (Haughton, 1873) although it is only within the past two years that his views have been recognized (Reynolds, 1949).

Haughton has shown that since tension in the tissues of a hollow organ is a function of the pressure within and the principal radii of curvature, the relative tensions in different regions of the uterus may be judged by knowing the radii of curvature in different parts. With respect to the fundus and the cervix, total tension in the tissues of the fundus is about double that in the cervix.

I need not here elaborate the significance of this conclusion. The effect of increasing the initial load or tension on a muscle, whether cardiac, striated or smooth, is to increase the contractile power of that muscle. We see, therefore, that Nature has deployed its greatest tension in that part of the uterus which is also thickest. For these two reasons, then, the action of the uterus in labour normally will be most powerful in the fundus.

The biochemical basis of uterine action in labour is a long, new, and most important part of the story of uterine action in labour. I must limit my remarks briefly to but one aspect of the subject.

The active contractile protein of muscle, called actomyosin, can be isolated from the living cell and its concentration and quality determined. When uterine muscle at term is so analysed, it is found (*see* Fig. 1) that the actomyosin is far more contractile than actomyosin from the non-pregnant uterus and far more contractile than that obtainable from uteri taken after irradiation menopause. Uterine actomyosin at term approaches in quality that of striated muscle (Csapo, 1948, 1950). Moreover, the concentration is far greater at term than it is in the non-pregnant uterus, but *only* in the fundus. Since actomyosin molecules are the "fingers" which do this work, it is clear that Nature places a metabolic advantage in the fundus for doing muscular work at term. We witness here a unique combination of morphology, biophysics and biochemistry working together to put greater contractile power in the fundus than elsewhere. Clearly, *fundal dominance* should be one of the outstanding features of the pattern of uterine contractility in labour. Is it?

Pattern of Uterine Contractility in Normal Labour

The only way which I know to analyse the patterns of uterine contractility is to record contractions from three or more points simultaneously. This we began to do in 1947, with the result shown in Fig. 2. A multichannel tokodynamometer was developed which recorded by three sensitive electric fingers (strain gauges) the differences in pressure between the centre and the circumference of each of the three rings (Reynolds, Hellman and Bruns, 1948). Since each unit is set to the same sensitivity, differences in intensity, frequency, duration, rhythm and other aspects of contractility in different regions of the uterus can be measured.

A sample of two contractions from a normal labour is shown in Fig. 3. Here we see the evidence of fundal dominance as the uterus itself writes it. The contractions are stronger and longer in the fundus than lower down in the uterus. There is a gradient of diminishing contractility from above, downward. This is a fundamental characteristic of all good labours. It will be noted that this pattern may be seen before labour, during Braxton-Hicks contractions, and in some cases of prodromal labour. The fact remains, however, that labours do *not* progress well without this pattern.

When data from 151 women were compiled and analysed by business punch card sorting machines, the average characteristics of normal, uncomplicated labours were determined (Hellman, Harris and Reynolds, 1950). The simplest summary of this is shown by the curves of Fig. 4. Here, work done by the fundus, mid-uterus, and the lower uterine segment in each third of the first stage of labour is shown, along with the curve of cervical dilatation and the frequency of contractions. How well the morphological, biophysical and biochemical factors are combined in the fundus to achieve their destined purpose!

The difference between the work done by the multiparous and the primiparous uterus in the first stage of labour is shown in Fig. 5. The basis of this difference is not known for a certainty. We may surmise, no doubt, that it is the result of improved fundal action in the face of less resistance to be overcome in multiparous women by uterine contractions after the cervix is dilated to 5 cm.

Patterns of Contractility in Abnormal Labour

One of the paramount problems in obstetrics arises when normal mechanics fail, and abnormal labour supervenes. The term "abnormal labour" is a clinical term, and requires definition. In the obstetrical clinic at Johns Hopkins Hospital, the definitions used and on which our work is based are as follows:

Normal labour begins when the cervix is 2 cm. dilated and it continues to full dilatation within fourteen hours in the case of primiparous, and eight hours in multiparous patients.

Prodromal labour is characterized by continued intermittent pain associated with uterine contractions at term without cervical dilatation but the pains continue into those of normal labour.

False labour is the same as prodromal labour, except that the pains subside before the cervical dilatation of labour begins.

Delayed labour is the result of cessation in the progress of cervical dilatation for more than one hour.

Prolonged labour results when full dilatation is not achieved until after fourteen hours in primiparous and eight hours in multiparous patients.

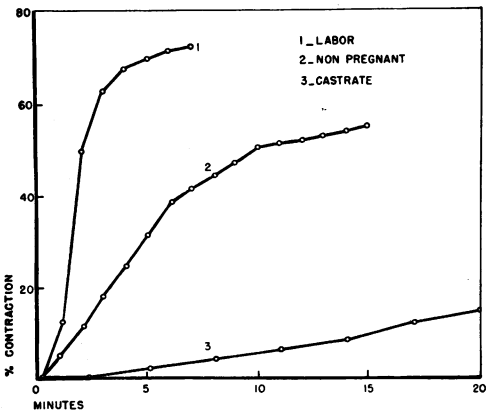

FIG. 1.—Behaviour of the contractile substance of the myometrium (actomyosin) when obtained under different hormonal conditions. Csapo (1950) modified from *Nature*.

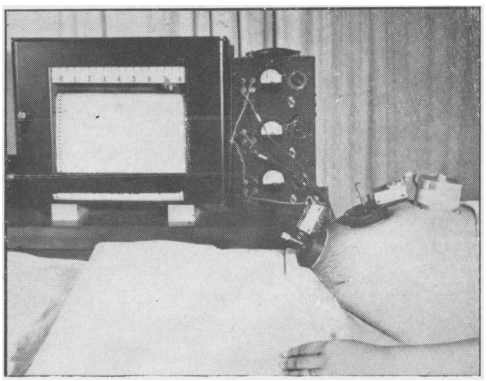

FIG. 2.—Picture of three "electric fingers" (strain gauges) in place on the abdomen of a woman in labour. A three-channel tokodynamometer (Figs. 2 and 3: Reynolds, 1951; courtesy of *Amer. J. Obstet. Gynec.*).

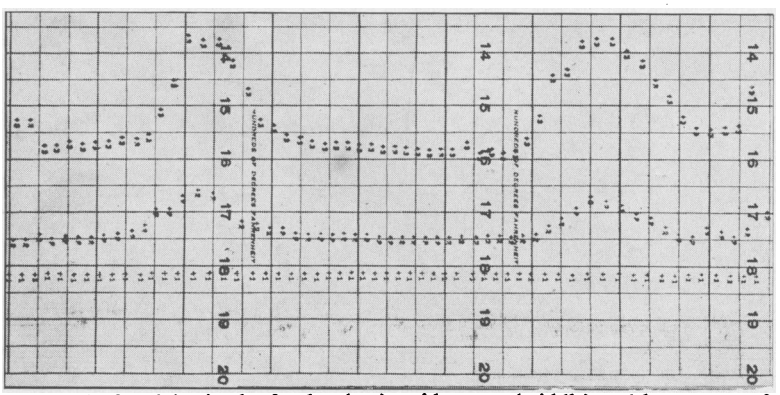

FIG. 3.—Record of activity in the fundus (top), mid-uterus (middle) and lower part of the uterus (bottom) during labour. Two contractions. Note contraction form, fundal dominance and inactive lower uterus. Vertical lines at 20-second intervals. Horizontal lines = 50 g. force on strain gauge.

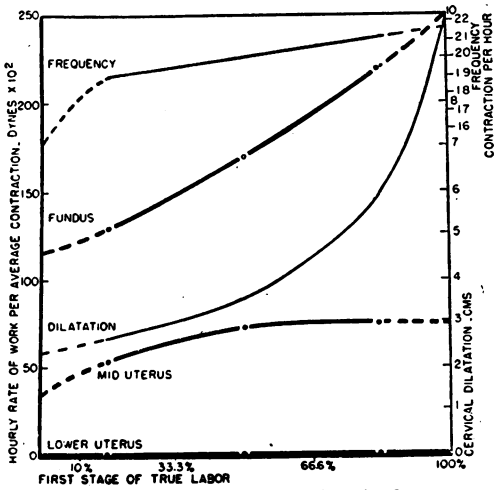

FIG. 4.—Work performed during the first stage of labour by the fundus, mid-uterus, and lower part of uterus. Based on 677 twenty-minute periods of observation in 151 normal women with uncomplicated labours.

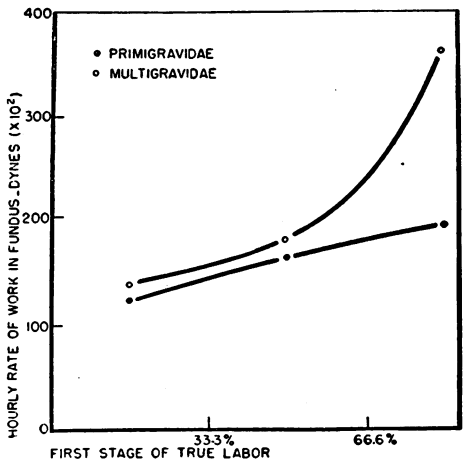

FIG. 5.—Difference in work done by the fundus in primiparous and multiparous women in the first stage of labour (Figs. 4 and 5: Hellman, Harris and Reynolds, 1950; courtesy of *Bull. Johns Hopk. Hosp.*).

Uterine inertia results when labour has been prolonged for more than twenty-four hours.

These definitions may be debatable, but within their limitations we have made numerous observations in each of these categories. I shall show you records from only a few, however, for the fundamental faults appear to be rather similar in all, the result depending merely upon *when*—before or during labour—the conditions giving rise to them develop. *Why* they develop is quite another matter. Most often, when abnormal uterine action occurs it is characterized by inco-ordination with too little pressure developing within the uterus to overcome the resisting cervix. These conditions are shown by the following examples, taken from a recent collaborative study which I had an opportunity to make with Professors Alvarez and Caldeyro in Montevideo (Alvarez, Caldeyro and Reynolds, 1950). We used internal (amniotic sac pressure) and seven-point external tokography simultaneously.

Normal labour (Fig. 6).—This record is shown because although the record came from a patient in clinically normal labour, we see, with seven-point recording, that co-ordination of

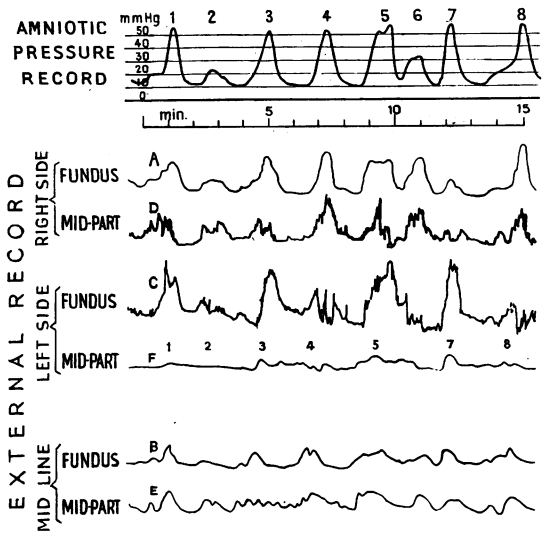

FIG. 6.—Simultaneous recording of intra-uterine pressure (amniotic sac) and six-channel external tokography. Section of record from *normal labour*. Note fundal dominance, synchronism, intensity of contraction, and pressure in the uterus well over 24 mm.Hg during uterine systole. Note two contractions (Nos. 5 and 6) in which there is asynchronism. There is right-sided dominance in contractions Nos. 2, 4, 6 and 8; left-sided dominance in contractions Nos. 1, 3, 5 and 7. Alvarez, Caldeyro and Reynolds (1950). Courtesy of *Surgery. Gynec. Obstet.*

uterine action is not perfect. Even so the absolute intra-uterine pressure is characteristic of good labour, averaging 38 mm. mercury during uterine systole. There is good fundal dominance on the right and left sides, but this is not so noticeable in the mid-line. There is good synchronization of different parts of the uterus except in the case of contraction numbers 5 and 6. There is some irregularity in rhythm, intensity and form. The right side predominates in contractions 2, 4, 6 and 8. The left side predominates in contractions 1, 3, 5 and 7. In normal labour, therefore, we observe a small proportion of contractions which are not completely co-ordinate. Enough are sufficiently co-ordinated, however, to effect cervical dilatation.

Prolonged labour is demonstrated by the portion of record shown in Fig. 7. This was obtained in a 39-year-old patient, gravida iv, para. iii. The first stage of labour lasted about eighteen hours. The intensity of intra-uterine pressure during uterine systole, averaging only 15 mm.Hg, was insufficient for rapid cervical dilatation. There was fundal dominance on the right side but not on the left. The lower part of the uterus gave evidence of contractility, while normally it is inactive. There was marked asynchronism between three regions of the uterus, which contracted independently of each other. These were: (1) each side of the fundus, (2) the mid-uterus on the left side, and (3) the lower right side of the uterus. There were marked irregularities in rhythm, intensity, and shape of the contractions. Much of the time, the amniotic pressure did not descend during uterine diastole to the normal level of 10 mm.Hg. Although, therefore, the contractions were weak, there was what would be called "hypertonia", but actually, the pressure was sustained by virtue of pressure exerted by the continuous effect of local and weak contractions in different parts of the uterus.

False labour, as shown in Fig. 8, is one of several general patterns of contractility which we have seen in this condition. The absolute intensity of pressure during uterine diastole in the uterus is low, averaging 9 mm.Hg. There is absence of fundal dominance because the contractions in the mid-uterus are stronger than those of the fundus. There is good synchronization of activity between the several parts of the uterus. Between contractions, the pressure descends to lower than normal levels, substantially *less* than 10 mm. mercury because the patient is not in labour. There is regularity in the rhythm of the contractions, but an irregularity in intensity which increased and decreased periodically throughout the period of observation.

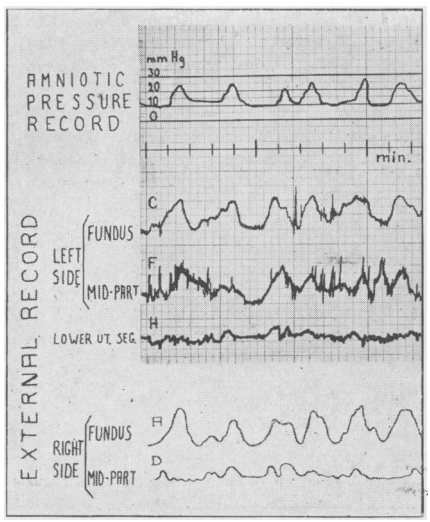

FIG. 7.—Simultaneous internal and external tokography in a case of *prolonged labour*. *See text* for analysis. Alvarez, Caldeyro and Reynolds (1950). Courtesy of *Surg. Gynec. Obstet.*

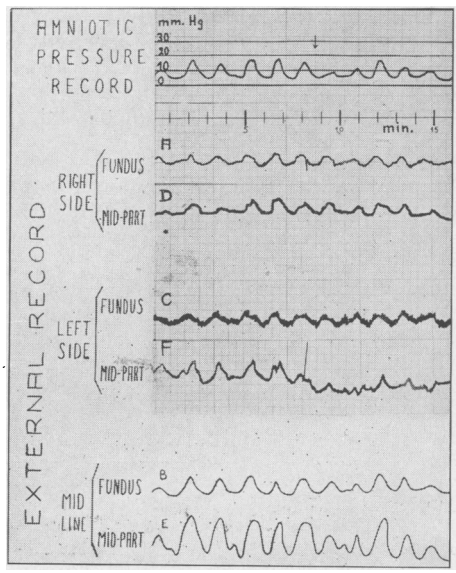

FIG. 8.—Simultaneous internal and external tokography in a case of *false labour*. *See text* for analysis. Alvarez, Caldeyro and Reynolds (1950). Courtesy of *Surg. Gynec. Obstet.*, **91**, 644 and 645.

More examples of these conditions, along with other abnormal types of labour, might be cited. However, we may summarize on the basis of what I have presented here what might be said of the whole. We have never seen a constriction ring, except as it develops intermittently during uterine contractions. With so-called "wooden" uterus in premature separation of the placenta, there is a sustained, high, intra-uterine pressure, but it is still associated with *rhythmic* activity in localized regions of the uterus without fundal dominance. In one case, this was seen in the mid-region of the uterus only, as strong rhythmic contractions continued at the top and bottom of the uterus. With onset of cervical dilatation, however, a well co-ordinated gradient of contractions was seen. In a few cases of false labour reverse gradients have been seen.

The characteristics of contractility which typify a normal labour may be briefly summarized by saying that there is normally good synchronization between different parts of the uterus with good fundal dominance. One side of the uterus may contract more strongly than the opposite side. When this is marked, or when the asynchronism is especially marked between the fundus, mid-uterus, and lower part of the uterus, the labour may be abnormal, *depending upon the degree to which asynchronism dominates the situation.* We may note that amniotic pressure sufficient to dilate the cervix is, in any moment, the sum of the pressures developed by the different contractions of the several parts of the uterus. This is influenced by two factors, namely, (1) the intensity of this activity at any one point, and (2) the synchronization of activity between the several contracting parts. The cervix dilates well *when the three characteristics of good contractility*, namely, (1) *good synchronization*, (2) *good fundal dominance*, and (3) *contractions of sufficient intensity*, are present. In normal labour these characteristics are seldom present all the time. When the deviation is marked and persistent, the labour becomes, clinically, abnormal, and the type of clinical characterization depends upon *when* the deviation begins with relation to the beginning of true labour.

We do not know why normal conditions do not always prevail. Factors of uterine growth, of physical forces, and uterine metabolism remain to be explored in relation to recent knowledge of the behaviour of the uterus in labour. I will mention but two points, in order to indicate promising avenues of investigation.

In the first place, my recent colleagues, Drs. J. S. Harris and I. H. Kaiser, have found that of all substances known to effect the contractility of the human uterus, epinephrine and nor-epinephrine are most potent. If these are given by intravenous drip at rates which could not possibly raise their concentration by as much as one-thousandth of a microgram, the normal patterns of contractility of the uterus in late pregnancy or in labour are destroyed. Epinephrine reduces or abolishes uterine contractility and nor-epinephrine raises tone (Kaiser, 1951; Kaiser and Harris, 1950). It is tempting to speculate that one or both of these substances may be secreted into the blood stream as a result of the pains of labour, especially in those women who are tense, or fearful of labour. While there is evidence that both substances are secreted under some conditions of stress, we do not know what the situation regarding this possibility is during labour. My colleague, Dr. Ramon Garcia, is at present engaged in such a study. In time we may know what fluctuations occur in blood epinephrine levels during normal and abnormal labours.

A record which was obtained on a hypnotized patient is shown in Fig. 9. This record was obtained last April on the service of Professor Rodriguez-Lopez of the Pereira Rossel

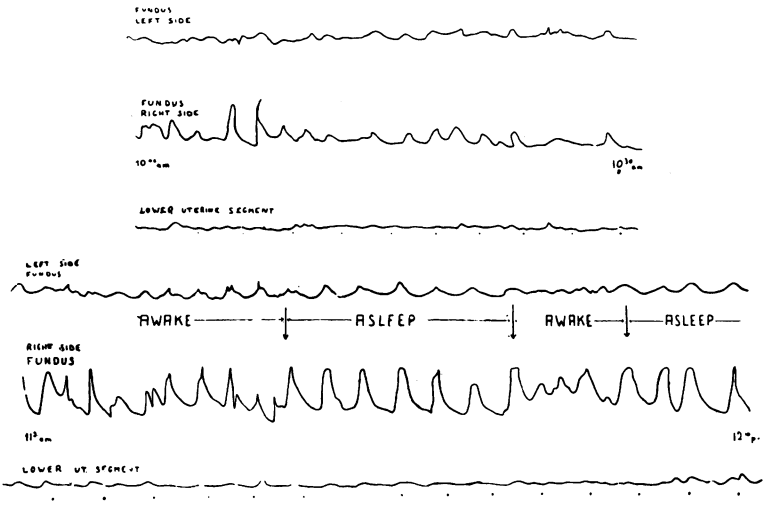

FIG. 9.—Record of the effect of induction of hypnotic sleep twice during a half-hour record in the first stage of labour (*see text*). Right-sided dystocia persisted, but the form, rhythm and intensity changed.

Hospital in Montevideo. During pregnancy, the suggestion had been made to the patient when under hypnosis that she would not experience pain in labour. Early in labour, while awake, her uterus exhibited weak, irregular contractions on the right side. The remainder of the uterus was inactive. Within an hour, the patient's cervix was found to be dilated to 5 cm. At this time, the early, right-sided activity was very strong and somewhat irregular as to form. The patient was then put in a state of deep hypnotic sleep, which I myself can testify was most effective. The rhythm and amplitude of contractions became remarkably regular in form and rhythm. The right-sided dystocia persisted, however. Even so, the cervix was dilated to 7 cm. within thirty minutes. On temporarily awaking, the earlier irregular pattern of contractility returned, but it improved promptly a second time during a second period of sleep. The record had to be terminated when, on palpation, the membranes ruptured and reflex bearing down movements became extreme. The cervix was now fully dilated. At no time did the patient have pain, except upon bearing down, when there was deep pain over the promontory of the sacrum.

What is the meaning of this observation on the effect of hypnotic sleep? I suspect that when more is known about this condition, we will discover what every obstetrician knows. We will find that sedation, analgesia, hypnosis, or psychological subordination such as may be achieved in so-called natural childbirth have one thing in common. They spare the uterus the physiological insult and consequence of painful stimuli in the organism, and these painful stimuli are, of course, an inevitable concomitant of the process of cervical dilatation during labour.

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Professor A. St. G. Huggett: Dr. Reynolds has put the results of his own work on pressure measurements and changes within the uterus: he has presented the relation between muscular structure and the tensile forces developed at different stages and, in addition, has outlined the possible application of the work of Szent-Gyorgi on actomyosin to this problem. Finally, he has shown the results of studies of the human uterus as illustrating the general principles he has outlined.

I will discuss certain physiological problems bearing on uterine contractility which await solution by the clinician and the laboratory worker.

Enlargement of the uterus during pregnancy.—The outstanding point about the uterus and its contents which distinguishes them from the other organs of the body is the time factor. The rate of change or the rate of growth, both in regard to the myometrium and the contents, is stupendous when compared with any other organ or the normal growth of the body. So far very little has been done to study the factors concerned in the muscular hypertrophy. The muscle fibres enlarge from lengths of 50μ to from 200 to 600μ in length; that is, a single nucleated cell lengthens to more than half a millimetre, visible to the naked eye. This occurs in a period of less than nine months.

We know that the enlargement is impossible in a spayed animal but can be maintained after double ovariectomy in the latter half of pregnancy in the human and in certain animals. Here the evidence shows that the œstrogen-progesterone complex of the ovaries is replaced by placental secretion of œstrogens, progesterone and chorionic gonadotrophin. We owe to the late Professor Newton (1949) the clear outline of the control of the extra-uterine metabolism of pregnancy by the placenta as a ductless gland, and to his colleague Dewar (1950), the importance of the progesterone secretion in this respect.

Nitrogen retention.—Young (1944, 1948) has shown how the growth hormone of the anterior lobe of the pituitary is probably identical with the diabetogenic hormone of the same organ. Over-action of the anterior pituitary results in growth distinguished by nitrogen retention and deposition accompanied by hypertrophy of the pancreatic islet tissue and insulin production, but if the islets fail to respond there is an excessive liberation of glucose with diabetes. In pregnancy there is what can best be described as unstable carbohydrate metabolism, glycosuria being easily produced on giving sugar. The hypertrophy of the pituitary would appear to be an essential for the retention of nitrogen and, presumably, for the formation of uterine muscle. It is clearly of importance for the factors concerned in good uterine development to be disentangled.

Response to hormones.—Since the reactions of the myometrium to œstrogens, to progesterone and to pituitrin are capable of great variation from species to species, and also at different phases of the œstrual or menstrual cycles, they are of importance in the proper understanding of the changes in pregnancy. From the point of view of the obstetrician a matter of considerable importance is the increase in sensitivity to pituitrin, a change which in the rabbit appears to depend upon the presence of progesterone.

In this connexion one is reminded of the classical experiment of Dale and Kellaway (1921) upon anaphylaxis. They showed that in a female guinea-pig made anaphylactic to a foreign protein, the uterus when excised was thrown into violent contraction in a water-bath when antigen was added to the bath. In other words, in the prolonged period between the first and last dose the antibodies formed had passed into the uterus.

Biochemical mechanisms of the myometrium.—It is clear, therefore, that to understand the mechanisms which are responsible for the growth of the myometrium in pregnancy and for the response of muscle, we need to evaluate the factors concerned in tissue growth and, secondly, to study the dynamic action of mass enzyme systems present in the uterine musculature and their response to hormonal influences. In invoking actomyosin, Dr. Reynolds has made a start. Perhaps Dr. Dorothy Needham will enlarge on this aspect of the subject.

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Dorothy M. Needham, Sc.D., F.R.S. (*Biochemical Laboratory, Cambridge*): To the biochemist the question of uterine contractility is interesting from several points of view. Let us consider first the proteins. It has to be remembered that, in the general theories of muscle contraction, the part played by actin and actomyosin is still obscure. We can feel certain that the fibrils of muscle consist mainly of polypeptide chains of the protein myosin, arranged with their long axes parallel to the fibril axis, and X-ray photographs indicate that actin is also incorporated in this regular molecular array. But we do not know how the myosin and actin interact *in vivo*; we do not even know whether actomyosin is present as such in the muscle before contraction, as postulated by Szent-Györgyi (1948), or whether the two proteins exist together in the resting muscle, only entering into combination on contraction, as suggested by Astbury (1950). It is therefore important to get this confirmation of the significance of actin from the study of the uterus, where the physiological change in the muscle to the more active state is marked by an increase in the proportion of actin present.

Again for the biochemist, the effect of œstrogen injections upon the uterine muscle of ovariectomized animals—the rapid increase in the amount of actomyosin + myosin present and the especially dramatic increase in the adenosinetriphosphatase (ATPase) activity (Csapo, 1950*a*)—open interesting possibilities. A comparatively simple hypothesis of the mechanism of action of the œstrogen upon the protein composition of the organ would be to suppose that the non-gravid uterus contains building stones in the shape of special proteins of much smaller molecular weight which, upon the appropriate stimulus, can be readily fitted together to form the contractile proteins themselves. Such a hypothesis would include an explanation for the great rise in ATPase activity while the actomysin + myosin has only risen slightly; it is true that normally the ATPase activity of muscle seems to reside in its myosin and that in general any changes in the myosin molecule, such as those which prevent its combination with actin, prevent also ATPase activity. It is, however, known that myosin can be broken down by careful treatment with trypsin (Perry, 1951) to a state where the molecules still show ATPase activity, but have become too small to show the characteristic effects of thread formation or increase in viscosity on mixing with actin. We may have here in the uterus reacting to œstrogen an example of the opposite case—the myosin molecules building up and passing through this same stage where ATPase activity is marked but possibility of actomyosin formation is restricted. It may be mentioned that skeletal and cardiac muscle contain a protein, tropomyosin (Bailey, 1948), present to the extent of about 2·5% of the total protein, of amino-acid composition similar in many respects to that of myosin, but of only about one-tenth the molecular weight. Bailey has made the suggestion that tropomyosin may be one of the units from which myosin is elaborated.

A consideration of Csapo's figures (Csapo, 1950*b*) shows that the actomyosin + myosin content of the uterus, even when gravid, is very low compared to skeletal muscle: only about one-quarter. Thus while in skeletal muscle actomyosin + myosin makes up about 66% of the protein, in uterus it is only about 20%. One would like very much to know something about the rest of the protein in the uterus; one might look, as I have suggested, for precursors of myosin and actin.

When we turn to the energy-providing metabolism of the uterus, we find that the information all points to the course of metabolism being similar to that in skeletal muscle, but the provision of energy-rich phosphate compounds is much less than in skeletal muscle—only one-tenth to one-twentieth even in the gravid uterus (Csapo, 1950*c*; Walaas and Walaas, 1950*a*). There is some evidence that in the uterus of ovariectomized rats, the injection of œstrogen leads to a slight but significant increase in ATP and creatinephosphate content; and also (from studies making use of radio-active ^{32}P) that there is increased turnover of acid-soluble P compounds after œstrogen in uterus muscle but not in skeletal muscle (Walaas and Walaas, 1950*b*).

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